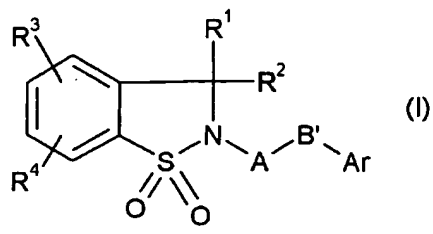
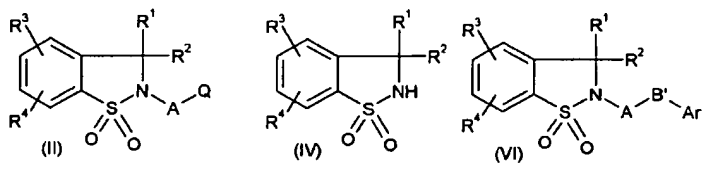


<p>99-303554/26 B02 BADI 97.10.22 BASF AG *DE 19746612-A1 97.10.22 97DE-1046612 (99.04.29) C07D 275/06, A61K 31/425, 31/44, C07D 417/04, A61K 31/445 New 2-substituted 1,2-benzisothiazole derivatives C99-089245 Addnl. Data: LUBISCH W, DULLWEBER U, STARCK D, STEINER G, BACH A, EMLING F, GARCIA-LADONA F J, TESCHENDORF H, WIECKE K</p>	<p>B(14-E10, 14-E11, 14-F2D, 14-J1, 14-J4) .3</p>  <p>(I)</p>
<p>NOVELTY 2-Substituted 1,2-benzisothiazole derivatives (I) and their acid salts are new.</p> <p>DETAILED DESCRIPTION 2-Substituted 1,2-benzisothiazole derivatives of formula (I) and their enantiomers, diastereomers, tautomers and acid salts are new.</p>	<p>R¹, R² = independently 1-6C alkyl; R³, R⁴ = independently H, 1-6C alkyl, OH, 1-6C alkoxy, F, Cl, Br, I, CF₃, NR⁵R⁶, CO₂R⁷, NO₂, CN, pyrrolo, or phenyl-(1-4C alkyl), which may itself be ring-substituted by F, Cl, Br, I, 1-4C alkyl, 1-4C alkoxy, CF₃, OH, NH₂, CN or NO₂; R⁵, R⁶ = independently H, 1-6C alkyl, benzoyl, CO₂-tert.-butyl, (1-4C alkyl)carbonyl or together form a 5- or 6-membered ring, which may contain a second N atom (e.g. piperazinyl); R⁷ = H or 1-6C alkyl;</p> <p style="text-align: right;">DE 19746612-A+</p>

<p>A = 1-10C alkylene or 2-10C alkylene containing one or more Z groups; Z = O, S, NR⁷, cyclopropyl, CHOH, or a double or triple bond; B = 4-piperidine, 4-(1,2,3,6-tetrahydropyridine), 4-piperazine or one of these rings N-bound to A via a methylene group; Ar = phenyl (optionally substituted by 1-6C alkyl, 1-6C alkoxy, OH, F, Cl, Br, I, CF₃, NR⁵R⁶, CO₂R⁷, CN or phenyl), tetralinyl, indanyl, other condensed aromatic moieties e.g. naphthalinyl (optionally substituted by 1-4C alkyl or 1-4C alkoxy), anthracenyl, or a 5- or 6-membered aromatic heterocycle with 1 or 2 O or N heteroatoms, which can be anellated with other aromatic groups.</p> <p>ACTIVITY Antidepressant; Nootropic; Tranquilizer; Vasodilator; Cerebroprotective; Relaxant.</p> <p>MECHANISM OF ACTION 5-HT_{1B} antagonist; 5-HT_{1A} antagonist (claimed).</p> <p>USE (I) are useful for treatment of depression (claimed). The</p>	<p>compounds can also be used to treat other disorders such as seasonal affective disorder, dysthymia, anxiety, panic attacks, obsessive-compulsive disorder, social phobia, post traumatic stress syndrome, dementia, amnesia, anorexia nervosa and bulimia nervosa. (I) can also be used to treat sexual dysfunction, hyperprolactinemia, blood vessel spasms (especially in the brain), hypertonia and gastrointestinal diseases associated with abnormal motility and secretion.</p> <p>ADVANTAGE Compounds (I) have high affinity for 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1A} serotonin receptors combined with very little influence on other types of receptor. The compounds' affinity for these receptors is more or less equal, or at least of the same order of magnitude; as a result, they show a good level of serotonin re-uptake inhibition which is of importance in treating depression.</p> <p>SPECIFIC COMPOUNDS Over 630 compounds (I) are specifically disclosed, e.g. 3,3-dimethyl-2-[3-(4-tetralin-5-yl-piperazin-1-yl)prop-1-yl]-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide (Ia).</p> <p style="text-align: right;">DE 19746612-A+/1</p>
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<p>99-303554/26</p> <p>ADMINISTRATION Daily dose is 1-100 mg/kg orally and 0.1-10 mg/kg parenterally.</p> <p>EXAMPLE To a solution of 1.64 g (6.0 mmol) 2-(3-chloroprop-1-yl)-3,3-dimethyl-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide in 40 ml DMF was added 1.1 g (5.2 mmol) 1-tetralin-5-ylpiperazine, 1.5 ml triethylamine and a trace of potassium iodide. The mixture was allowed to react for four hours at 100 °C and was then poured onto ice/water and filtered. The crude product was purified by crystallization from isopropanol to give 1 g (43 %) (Ia).</p> <p>TECHNOLOGY FOCUS Organic Chemistry - Preparation: (I) are prepared by: (1) Reacting a compound of formula (II) with a compound of formula H-B-Ar (III) (2) Reacting a compound of formula (IV) with one of formula Q-A-B-Ar (V) (3) Coupling of a compound of formula (VI) with (III) by reductive amination.</p>	 <p>(II) (IV) (VI)</p> <p>H-B-Ar (III)</p> <p>Q = a cleavable group e.g. Cl, Br, I, alkanesulfonyloxy or arylsulfonyloxy. (53pp2510DwgNo.0/0)</p> <p style="text-align: right;">DE 19746612-A/2</p>
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